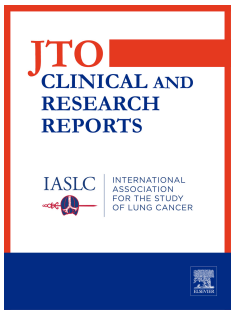

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Expansion Phase 1 Study of Pegargiminase Plus Pemetrexed And Cisplatin in Patients With ASS1-Deficient Mesothelioma: Safety, Efficacy and Resistance Mechanisms

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ABSTRACT

INTRODUCTION: Pegargiminase (ADI-PEG 20; ADI) degrades arginine and potentiates pemetrexed cytotoxicity in argininosuccinate synthetase 1 (ASS1)-deficient malignant pleural mesothelioma (MPM). We conducted a phase 1 dose-expansion study at the recommended phase 2 dose (RP2D) of ADI-PEG 20 with pemetrexed (Pem) and cisplatin (Cis) (ADIPemCis), to further evaluate arginine-lowering therapy in ASS1-deficient MPM and explore mechanisms of resistance.

METHODS: Thirty-two chemonaïve patients with ASS1-deficient MPM (11 epithelioid;10 biphasic;11 sarcomatoid) received weekly intramuscular pegargiminase (36 mg/m^2) with Pem (500 mg/m^2) and Cis (75 mg/m^2) intravenously, every three weeks (six cycles maximum). Maintenance pegargiminase was permitted until disease progression or withdrawal. Safety, pharmacodynamics, immunogenicity, and efficacy were determined. Biopsies were performed in progressing patients to explore mechanisms of resistance to pegargiminase.

RESULTS: Treatment was well-tolerated. Most adverse events (AEs) were Grade 1/2, while four non-hematologic Grade 3/4 AEs related to pegargiminase, were reversible. Plasma arginine decreased while citrulline increased; this was maintained by 18 weeks of ADIPemCis therapy. The disease control rate in thirty-one evaluable patients was 93.5% (n=29/31; 95% CI 78.6% - 99.2%), with a partial response rate of 35.5 % (n=11/31; 95% CI 19.2% - 54.6%). The median progression-free and overall survivals were 5.6 (95% CI, 4.0 to 6.0) and 10.1 (95% CI, 6.1 to 11.1) months, respectively. Progression biopsies on pegargiminase revealed a statistically significant influx of macrophages (n=6; p=0.0255) and patchy tumoral ASS1 re-expression (n=2/6). Additionally, we observed increased tumoral PD-L1 – an ADI-PEG20

inducible gene – and the formation of CD3-positive T lymphocyte aggregates on disease progression (n=2/5).

CONCLUSIONS: The dose-expansion of ADIPemCis confirmed high clinical activity and good tolerability in ASS1-deficient poor-prognosis mesothelioma, underpinning an ongoing phase 3 study (clinicaltrials.gov NCT02709512). Notably, resistance to pegargiminase correlated significantly with macrophage recruitment and – along with the tumor immune microenvironment – warrants further study to optimize arginine deprivation for the treatment of mesothelioma.

KEYWORDS: Arginine; ASS1; ADIPemCis; Mesothelioma; Macrophages

INTRODUCTION

Malignant pleural mesothelioma (MPM) is predominantly an asbestos-driven thoracic tumor notable for its chemoresistance and poor prognosis. Median survivals range from 3.5 and 6.6 months for the non-epithelioid, sarcomatoid and biphasic variants, respectively, and up to 18 months for the epithelioid subtype.[1,2] No new front-line therapies for mesothelioma have been licensed since the antifolate pemetrexed with cisplatin in 2004.[3]

In preclinical studies we identified arginine depletion as a rational antimetabolite strategy that targets mesothelioma cells displaying epigenetic inactivation of the urea cycle enzyme, argininosuccinate synthetase 1 (ASS1).[4] Arginine deprivation impacts multiple biosynthetic pathways including proteins, polyamines, nucleotides, and nitric oxide, emphasizing an essential role for the amino acid in the growth or auxotrophy of mesothelioma and other cancers.[5-7] Consequently, bacterial-derived pegylated arginine deiminase (ADI-PEG 20, ADI or pegargiminase) or bioengineered forms of human arginase are currently in development for patients with a range of advanced malignancies.[8-10]

Clinically, pegargiminase, which degrades arginine into citrulline and ammonia, improved progression-free survival in patients with ASS1-deficient MPM in the ADAM study, representing the first biomarker-driven randomized trial of arginine deprivation versus best-supportive care in cancer.[11] Moreover, ASS1 was prognostic with ASS1-deficient disease conferring a worse survival compared with ASS1-proficient disease, consistent with data linking dysregulation of urea cycle enzymes to accelerated tumorigenesis.[5,11] Additionally, when ADI-PEG 20 was combined with pemetrexed and cisplatin chemotherapy (ADIPemCis) in the phase I dose-escalation TRAP (Tumors Requiring Arginine to Assess ADI-PEG 20, Pemetrexed and cisplatin) study a 100% disease control (78% partial response) rate was observed in nine patients with thoracic cancers (lung adenocarcinoma and MPM), including four of five patients with non-epithelioid MPM.[12] Nevertheless, despite prolonged suppression of plasma arginine and a

reciprocal increase in citrulline, patients progressed on ADIPemCis therapy, thereby implicating tumoral, rather than drug-innate, mechanisms of resistance to arginine deprivation.

First, re-expression of ASS1, and thus the recycling of citrulline to arginine, following long-term culture of tumor cell lines including MPM cells in ADI-PEG 20, has been identified as a viable resistance mechanism with confirmatory studies in patients with melanoma.[13-15] Secondly, autophagy (the degradation and recycling of cellular components) is known to protect ASS1-negative MPM cells from arginine depletion.[16] Thirdly, the tumor microenvironment may also mediate cancer cell resistance to arginine withdrawal however this has not been addressed specifically in the context of pegargiminase. Tumor-associated macrophages (TAMs), in particular, constitute up to 30% of the total cell population of mesothelioma and play a key role in asbestos-mediated tumorigenesis.[17-20] As such, TAMs might also play a role in resistance to arginine deprivation therapy.

Here, we treated a dose-expansion cohort of thirty-two patients with ASS1-deficient MPM at the recommended phase 2 dose (RP2D) of ADI-PEG 20 (36mg/m^2) in combination with standard doses of pemetrexed and cisplatin. The main aims of this phase 1 dose-expansion study were to define further the safety and preliminary activity of the ADIPemCis triplet in patients with MPM, and to elucidate mechanisms of resistance to arginine deprivation by analyzing patients' tumors at progression.

PATIENTS AND METHODS

Patient Eligibility

Patients were aged 18 years or over, chemonaive with histologically proven ASS1-deficient advanced MPM (see Beddowes et al for methods).[12] Additional eligibility included an ECOG performance status 0 or 1, no major co-morbidities, a minimum expected survival of 3 months, and measurable disease by modified Response Evaluation Criteria in Solid Tumors criteria (RECIST) for MPM. Exclusion criteria included recent major surgery, history of another active primary cancer, and prior therapy with pegargiminase. All patients signed written informed consent.

Study Design and Treatment

This dose-expansion multicentre phase 1 study evaluated the RP2D of 36 mg/m^2 weekly intramuscular ADI-PEG 20 plus three-weekly 75 mg/m^2 cisplatin and 500 mg/m^2 pemetrexed derived from the previous dose-escalation TRAP study.[11] Standard premedication was administered, including oral dexamethasone, daily folic acid, and 1000μg intramuscular (IM) hydroxycobalamin every nine weeks. The initial dose of IM ADI-PEG 20 was administered 48 hours before the first dose of cytotoxic drugs. Patients received up to 6 cycles (18 weeks) of ADIPemCis chemotherapy and could continue on maintenance pegargiminase until disease progression or withdrawal. Blood samples were taken at baseline, during ADIPemCis chemotherapy, and on disease progression or withdrawal from the study. Tumor biopsies were required at baseline and were optional at disease progression.

The primary objective of the dose-expansion study was to determine the safety and tolerability, and to estimate the preliminary efficacy of ADIPemCis in patients with ASS1-

deficient MPM. Secondary objectives included measuring pharmacodynamics, immunogenicity, and exploration of resistance mechanisms to pegargiminase.

Safety

Evaluation of safety was based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, vital signs, physical examination, ECGs, and laboratory blood analyses.

Pharmacodynamic and Efficacy Evaluations

Blood samples were analyzed by Polaris Pharmaceuticals, Inc., (San Diego, California, USA) for arginine and citrulline levels and anti-ADI-PEG 20 antibody titres, as described previously.[11,12] Efficacy was assessed by computed tomography imaging using modified RECIST every 6 weeks while on ADIPemCis and then every 2 months on maintenance pegargiminase.

Patient tumor Immunohistochemistry (IHC)

Tumor biopsies were assessed for ASS1 expression using mAb 195-21-1 from Polaris Pharmaceuticals, Inc., San Diego, California, USA. Infiltrating $CD68^{pos}$ macrophages were identified using a murine anti-human antibody (KP-1) and quantified as a percentage of the number of malignant cells, taking an average from five high-power fields at 400x magnification. PD-L1 (Cell Signalling E1L3N and Ventana-Roche SP-263 antibodies) and CD3 (Ventana-Roche 2GV6 antibody) expression was performed subsequent to the CD68 staining using residual tissue. PD-L1 was scored as a percentage of positive tumour cells and CD3 summarised descriptively.

Statistical analyses

No formal sample size calculation was made for the dose-expansion TRAP study in patients with MPM, which aimed to recruit up to 30 patients as per protocol. AEs were collated, and response rates, PFS and OS characterized according to MPM subtype. Patients' tumour biopsies were analyzed using a paired t-test in GraphPad Prism version 8.3.1. A p-value of <0.05 was considered to be statistically significant. This trial is registered with clinicaltrials.gov, number NCT02029690.

Ethical considerations

The clinical protocol (ClinicalTrials.gov identifier NCT02029690) was approved by Leeds East Research Ethics Committee (14/YH/0090) and was sponsored by Polaris Pharmaceuticals, Inc.

RESULTS

Patient Demographics

Patient enrolment into the dose-expansion study began in February 2015 and was completed in May 2016. Ninety-three patients were screened to recruit thirty-two patients with ASS1-deficient MPM treated with ADIPemCis: eleven with epithelioid, ten with biphasic, and eleven with the sarcomatoid subtype (Fig. 1). The protocol amendment for the dose-expansion cohort specified the enrollment of thirty patients at the RP2D; one patient was deemed ineligible and replaced due to occult malignant melena and an additional patient consented as the study recruitment was closing. All subjects were included for the safety analysis and thirty-one for the efficacy analysis (Table 1).

Safety

Consistent with the prior dose-escalation study, ADIPemCis treatment was well-tolerated (Supplementary Tables 1 and 2). Adverse events were reported in 24/32 (75%) patients, the majority of which were related to cisplatin and/or pemetrexed, namely 22/32 (68.8%), and to pegargiminase in 12/32 (37.5%) patients. The majority were Grade 1 or 2 (116/137 or 84.7%) particularly nausea and vomiting and decreased blood counts, with the remainder Grade 3 or 4 only (21/137 or 15.3%). There were four non-haematologic Grade 3 or 4 adverse events related to pegargiminase: increased alkaline phosphatase, hyperuricaemia, skin rash and posterior reversible encephalopathy syndrome. The latter was unexpected and occurred in a patient with a sarcomatoid mesothelioma presenting with agitation and characteristic MRI features during maintenance pegargiminase. He recovered completely following anxiolytics, steroids and pegargiminase discontinuation (Supplementary Fig. 1).

Pharmacodynamics

Pegargiminase decreased plasma arginine with a reciprocal increase in plasma citrulline levels in patients (Fig. 2A). As reported in the dose-escalation cohort, plasma levels of the amino acids remained differentially altered compared with pre-treatment levels by 18 weeks, despite a concomitant increase in anti-ADI-PEG 20 antibodies (Fig. 2B).

Efficacy

ADIPemCis treatment induced a high disease control rate of 93.5% (n=29/31; 95% CI 78.6% - 99.2%), with a partial response rate of 35.5 % (n=11/31; 95% CI 19.2% - 54.6%) in a cohort of patients enriched by ASS1 loss for non-epithelioid MPM (Fig. 2C, D). The median progression-free survival (PFS) and overall survival (OS) were 5.6 (95% CI, 4.0 to 6.0) and 10.1 (95% CI, 6.1 to 11.1) months, respectively (Fig. 3A, B). Subsequently, 11/31 (35.5%) patients received anti-PD1 therapy with pembrolizumab achieving stable disease in one patient (9.1%), while nine patients had progressive disease (81.8%) and one patient was non-evaluable (9.1%). PD-L1 expression prior to treatment was available in 9/11 patients ranging from 0% (n=4) to 1-30% (n-5). Due to rapidly progressive disease a minority of patients received second-line and subsequent therapies (vinorelbine and/or gemcitabine).

Exploratory Tumor Biopsies

To understand drug resistance six patients on pegargiminase therapy consented to a tumor rebiopsy at progression allowing a comparison with the pre-treatment biopsies. ASS1 levels increased in a subpopulation of MPM cells in two of six patients with epithelioid and sarcomatoid disease during cycles 5 and 6 of ADIPemCis (Fig. 4A). There was a significant

increase of CD68^{pos} ASS1^{pos} macrophages at disease progression in ASS1^{neg} tumor areas, which included four patients receiving maintenance pegargiminase for up to 18 months ($p=0.0255$; $n=6$; Fig. 4B, C). Due to patchy ASS1 tumoral re-expression seen in two patients only we were unable to quantify the amount of macrophage infiltration specifically in ASS1^{pos} tumor areas. We also noted an increase in tumoral PD-L1 expression and clustering of CD3^{pos} T lymphocytes within MPM tumor cell islands in two of five patients with available tissue for IHC (Fig. 5). In the remaining three patients we detected variable effects on PD-L1 expression and/or T cell localisation at disease progression (Supplementary Table 3).

DISCUSSION

In this ASS1 biomarker-led study we observed good tolerability and a high rate of disease control in patients enriched with poor-prognosis MPM treated with the RP2D of ADIPemCis, expanding on the preliminary signal in the dose-escalation trial. Nonetheless, tumor progression on pegargiminase was universal, and instead of widespread ASS1 tumoral re-expression, correlated significantly with macrophage infiltration on rebiopsy, pointing to a stromal-mediated resistance pathway that may be leveraged to optimise arginine-depleting cancer therapeutics. We also describe induction of tumoral PD-L1 expression and modulation of T lymphocytes, which segues into the developing area of mesothelioma immunotherapy.

Toxicities were mostly Grade 1 or 2 nausea and vomiting, haematologic and injection skin reactions, while grade 3 or 4 events were manageable and reversible. There was only one serious Grade 3 toxicity attributed to pegargiminase maintenance therapy, namely posterior reversible encephalopathy syndrome, a known complication of several bio-chemotherapies, including bevacizumab and the enzyme therapeutic, asparaginase, but described here for the first time with arginine deprivation.[21]

The median OS and PFS of 10.1 and 5.6 months, respectively, are encouraging in a patient cohort enriched for poor-prognosis ASS1-deficient disease. Biomarker screening selected 2-3 times as many patients with non-epithelioid compared to epithelioid disease, consistent with prior datasets for ASS1 loss in MPM, and accounting for the unusually high rate of patients enrolled with non-epithelioid disease (65.6%).[4,12,22] The median OS for epithelioid disease was 11.1 months and lower than that reported in recent phase 3 studies with median OS of 16.1 months for patients with predominantly epithelioid disease (81-97%) in the standard chemotherapy groups (LUME-meso and MAPS trials).[23,24] Moreover, twice as many patients were alive at 15 months with biphasic compared with epithelioid disease (40% vs 20%),

indicating that the latter subgroup is at the aggressive end of the spectrum, and concurring with poor-prognosis epithelioid disease defined by nuclear grading and p16 loss on multivariate analysis.[25,26]

Notably, the 8.2 month median OS for non-epithelioid disease compares favourably with the recent SWOG S0905 trial reporting a median OS of 6.3 months for PemCis plus placebo or 6.5 months for PemCis plus the VEGFR antagonist, cediranib (n=23; non-epithelioid).[27] Additionally, we observed a doubling of the median survival (6.5 versus 3.5 months), and a 3-fold increase in survival at 12 months (30% vs 10%), compared to historical controls for sarcomatoid mesothelioma.[1,26] Although response assessment in mesothelioma is challenging, and reported infrequently in trials for non-epithelioid disease, the 93.5% disease control rate is encouraging and consistent with the earlier dose-escalation study.[12] Collectively, these data benchmarked the design of the ATOMIC-meso study, which transitioned from phase 2 to phase 3 earlier this year after successful recruitment of 176 patients with non-epithelioid mesothelioma; a further 210 patients are being enrolled to report on the primary endpoint of OS (ClinicalTrials.gov identifier NCT02709512).

A key exploratory aim of the dose-expansion study was to understand resistance to ADI-PEG20 based therapy by sampling patients' tumors on progression. Six patients consented to repeat biopsies which were incorporated into patient management, most commonly for control of a recurrent pleural effusion. Due to limited baseline tissue, we analyzed ASS1 status followed by CD68 expression on macrophages, and lastly PD-L1 expression and CD3 expression on lymphocytes. Patchy induction of tumoral ASS1 was identified in two patients, supporting a limited role for ASS1 re-expression as a mechanism of resistance to pegargiminase as identified in long-term MPM cell line culture under ADI-PEG 20.[13] This contrasted with a robust and statistically significant influx of $CD68^{pos}$ $ASS1^{pos}$ macrophages in ASS1-deficient tumoral regions, which is of particular interest since myeloid cells are known to express abundant ASS1

under proinflammatory cytokine control.[28] Moreover, arginine metabolism is a critical component of macrophage function, including nitric oxide synthesis for pathogen recognition and polyamine synthesis for wound healing.[29] Interestingly, we also observed an influx of $CD68^{pos}$ $ASS1^{pos}$ macrophages in ASS1-deficient tumoral regions in two rebiopsied patients in a separate expansion study of ADIPemCis in patients with NSCLC; or, p=0.0079 for the entire thoracic patient cohort of ADIPemCis (Supplementary Figure 2).[30] Separately, we have identified a novel mechanism whereby ADI-PEG 20 induces several chemoattractant proinflammatory cytokines from MPM cells triggering resistance to arginine deprivation via macrophage-derived argininosuccinate, the immediate precursor for arginine synthesis.[†]

Our analysis of resistance was limited by the availability of patient tissue, especially the polarisation of the infiltrating $CD68^{pos}$ $ASS1^{pos}$ macrophages (i.e. M1 and M2 macrophage subtypes) and the potential role of autophagy which will require further study.[31,32] Indeed, autophagy was inferred in a separate expansion cohort study of ADIPemCis in glioblastoma multiforme with a patient exhibiting prolonged remission on maintenance ADI-PEG 20 with quinine sulphate, an antimalarial autophagy inhibitor, and on a background of durable arginine depletion (20.8 months).[33] Indeed, autophagy as a contributory resistance mechanism has been described preclinically in various cancer cell lines including MPM cells, and is similarly abrogated with chloroquine.[16,34,35] Finally, pharmacologic resistance due to neutralising antibodies to ADI-PEG 20 cannot be excluded entirely, as arginine levels, while persistently low compared to pre-treatment levels, increased at the end of the 18 week sampling period (with reciprocal changes in citrulline). Nonetheless, the pharmacodynamic changes were durable in the dose-escalation ADIPemCis study, which reported a higher median OS of 13.9 months in patients with thoracic cancers; these inter-study differences may be explained in part by a variation in the amount of blood sampling performed at each timepoint due to earlier subject

[†] Manuscript under review

withdrawal in the current study (Supplementary Table 4).[12] It is also significant that blood draws were performed weekly and just prior to ADI-PEG 20 dosing, reflecting static rather than dynamic changes in amino acid levels.

The limited analysis of tumoral PD-L1 expression and CD3 lymphocytes at progression in the remaining five biopsies was insufficient to draw firm conclusions. However, the upregulation of PD-L1 and CD3 lymphocytes in two of the five patients on rebiopsy is consistent with earlier preclinical work of ADI-PEG20 inducing PD-L1 in tumor cell lines and T cell infiltration in syngeneic tumor mouse models.[36] Recently, a phase 1 study of pegargiminase and pembrolizumab in solid tumors completed accrual with on-treatment biopsies that evaluate the effects of pegargiminase specifically on T cell markers in the tumor microenvironment prior to PD-1 blockade (clinicaltrials.gov identifier NCT03254732).[37] Although a third of patients received pembrolizumab on progression (6/11 epithelioid and 5/11 non-epithelioid), the disease control rate of 11.1% (n=1/11; biphasic disease) was disappointing and lower than that reported in larger patient studies of PD-1/PD-L1 blockade in mesothelioma (47%-72%).[38-41] However, four of the pembrolizumab-treated patients expressed PD-L1 <1% (n=4/9 or 44.4), which is known to correlate with lower responses to PD-1 blockade compared to >1% PD-L1 MPM expression (Supplementary Table 5).[41] Furthermore, the influx of tumor-associated macrophages reported above may have contributed potentially to a more immunosuppressive environment constraining PD1-based immune checkpoint therapy.[42]

Clearly, further dissection of the complex effects of arginine deprivation on the mesothelioma microenvironment will be needed to understand the role of ADI-PEG20 in the context of mesothelioma immunotherapy.[43-45] Moreover, studies in urea cycle dysregulated cancers suggest that biomarker analysis will be of increasing importance in guiding prognosis and therapeutic response to arginine-based therapeutics.[46] We propose that the macrophage influx may be exploited pharmacologically to optimise arginine deprivation as a novel anti-

metabolite therapy for mesothelioma and other treatment-resistant cancers. Indeed, several approaches are under clinical evaluation including, CSF-1R, CXCR2, CD47 (‘don’t eat me’) and PD-1 antagonists, to retarget TAMs for tumor cell killing.[47-52]

In summary, ADIPemCis is safe and active in an expansion cohort of patients with aggressive ASS1-deficient MPM and a phase 3 trial is underway. Our data also provide novel insights into resistance pathways to arginine deprivation, going beyond tumoral ASS1 re-expression, namely macrophage trafficking. Validation of this innate-immunometabolic relationship, by targeting macrophages alongside tumor cells with pegargiminase therapy, has the potential to improve patients’ outcomes with mesothelioma and other arginine-auxotrophic cancers.

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FIGURE LEGENDS

Figure 1. CONSORT diagram

Figure 2. Pharmacodynamics and Response (A) Pharmacodynamics of arginine and citrulline in patients treated with ADIPemCis. Serum [arginine] and [citrulline] are shown by week of treatment (means ± SEM). **(B)** Serum levels of anti-ADI-PEG 20 antibodies in all patients by week of ADIPemCis (Mean ± SEM); Ab, Antibody. **(C)** Waterfall plot of response by modified RECIST to ADIPemCis. **(D)** Spider plots showing response duration to ADIPemCis.

Figure 3. Survival outcomes (A) Progression-free survival by MPM histological subtype. **(B)** Kaplan-Meier survival estimates by MPM histological subtype.

Figure 4. Baseline and progression biopsies analyzed for ASS1 and CD68 (A) Tumoral ASS1 re-expression at progression noted in two patients (200x magnification; epithelioid and sarcomatoid). **(B)** Increase in $CD68^{pos}$ macrophages at disease progression in ASS1-deficient tumoral regions (n=6; p=0.0255; paired t-test); 2 epithelioid, 1 sarcomatoid and 3 biphasic tumors (N.B. one epithelioid tumor was reclassified as biphasic on surgical rebiopsy). **(C)** Representative serial sections of epithelioid, biphasic and sarcomatoid MPM at baseline and progression stained for ASS1 and CD68, showing the increase in $ASS1^{pos}CD68^{pos}$ macrophages at progression (200x magnification).

Figure 5. Baseline and progression biopsies analyzed for PD-L1 and CD3 Modulation of PD-L1 expression and $CD3^{pos}$ lymphocytes in two patients at progression (200x magnification; epithelioid and biphasic). PD-L1 increased from 10 to 30% (in epithelioid disease) and 0 to 5% (in biphasic disease) with clustering of $CD3^{pos}$ T cells in both patients at progression.

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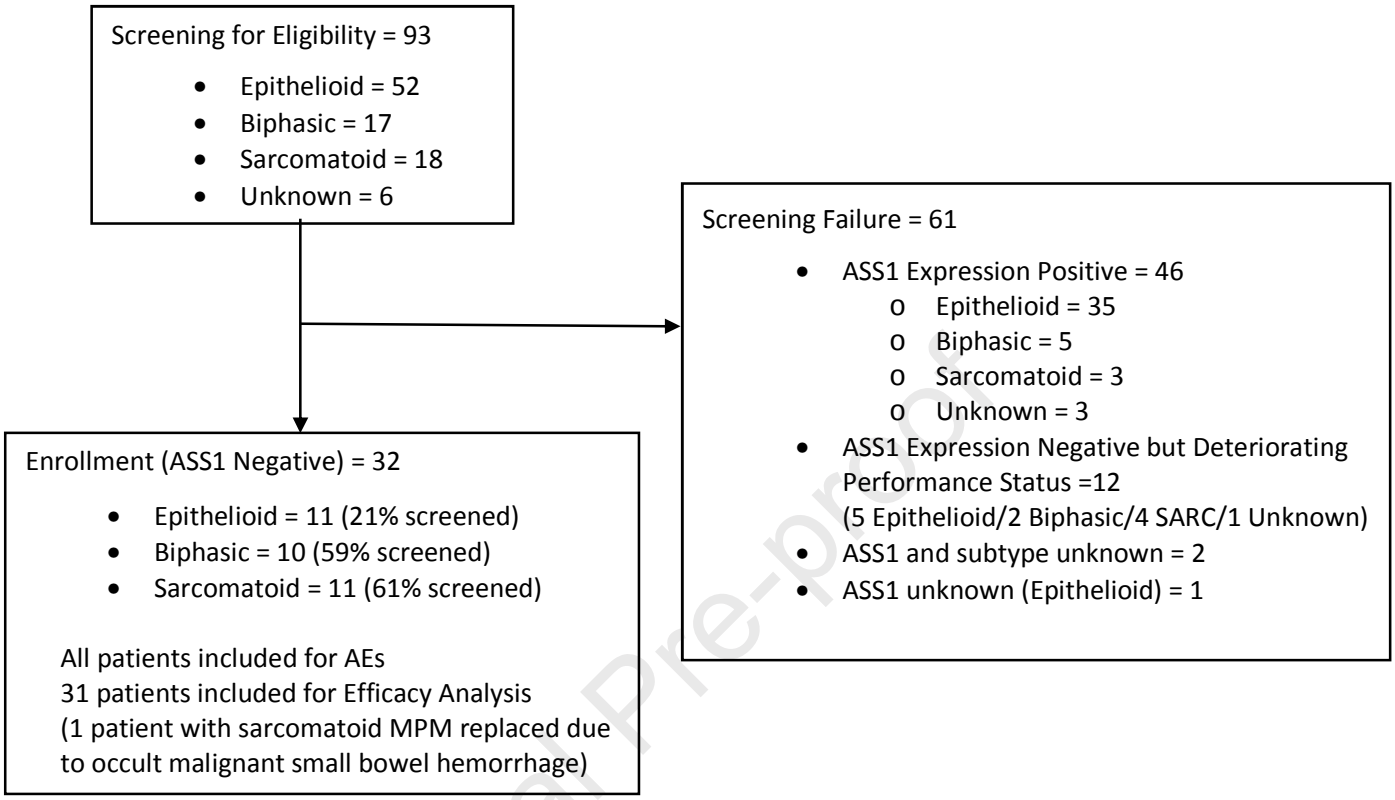
Table 1. Demographics

Characteristic	Epithelioid (n=11)	Non-Epithelioid (n=21)	
		Biphasic (n=10)	Sarcomatoid (n=11)*
Age, median (range), y	67 (61-77)	66 (49-82)	68 (58-79)
Sex			
Male	10	8	11
Female	1	2	0
Performance status			
0	1	1	0
1	10	9	11
Previous surgery			
Yes	3	2	1
No	8	8	10
Disease Stage#	1A (n=1); 1B (n=4) II (n=1) IIIA (n=2) IV (n=3)	1A (n=1) 1B (n=6) IIIA (n=1) IV (n=2)	1B (n=6) II (n=1) IIIA (n=1) IV (n=3)
Time on study treatment, median (range), months	4.6 (0.5-7.0)	6.1 (1.9-18.0)	4.1 (1.2-5.9)

#Eighth TNM classification for mesothelioma.



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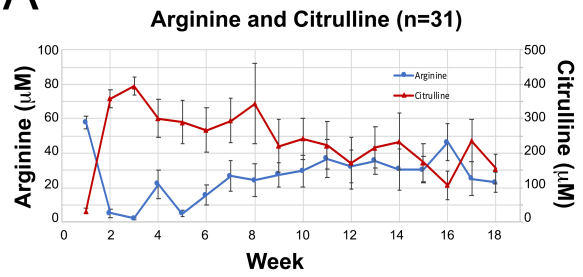

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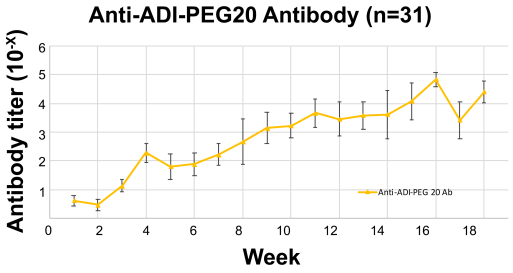

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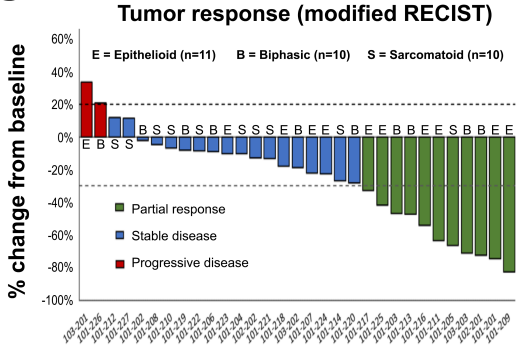

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